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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAJIV SHAH and BAHAR REGHABI

Appeal 2009-011224
Application 10/035,918
Technology Center 1600

Decided: March 22, 2010

Before LORA M. GREEN, RICHARD M. LEBOVITZ, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 by the Patent Applicant from the Patent Examiner's rejections of claims 1, 3-8, 10-24, and 44-46. The Board's jurisdiction for this appeal is under 35 U.S.C. § 6(b). The rejection is affirmed.

STATEMENT OF THE CASE

The claims are drawn to methods of screening for mutated glucose oxidase ("GO") enzymes which have peroxide resistant properties. Glucose oxidases are utilized in biosensors to detect glucose (Spec. 3:1-14). Hydrogen peroxide is produced as a by-product of the enzymatic reaction (*id.* at 3:15-16). The peroxide molecule inactivates GO, limiting the biosensor's lifetime (*id.* at 3:20 to 4:2). To address this problem, a "directed evolution" technique is described by the inventors which utilized genetic engineering techniques to produce enzymes with improved peroxide-resistant properties (*id.* at 5-6).

The claims 1, 3-8, 10-24, and 44-46 are pending. The claims stand rejected by the Examiner as follows:

1. Claims 1, 3-5, 12-15, 18-24, 44, and 45 under 35 U.S.C. § 103(a) as obvious in view of Valdes (*In Vitro and In Vivo Degradation of Glucose Oxidase Enzyme Used for an Implantable Glucose Biosensor*, Diabetes Technology & Therapeutics, Vol. 2, No. 3, pp. 367-376 (2000)), Cherry (*Directed evolution of a fungal peroxidase*, Nature Biotechnology, Vol. 17, pp. 379-384 (1999)), and Hatzinikolaou (*A new glucose oxidase from Aspergillus niger: characterization and regulation studies of enzyme and gene*, Applied Microbiology & Biotechnology, Vo. 46, pp. 371-381 (1996)) (Ans. 4);

2. Claim 16 and 17 under 35 U.S.C. § 103(a) as obvious in view of Valdes, Cherry, Hatzinikolaou, and Misonix (*Ultrasonic Liquid Processors*, Cole Parmer Catalog, p. 2112) (Ans. 7); and

3. Claims 6-8, 10, 11, and 46 under 35 U.S.C. § 103(a) as obvious in view of Valdes, Cherry, Hatzinikolaou, Wagner (EP 0 251 475 A1, Jan. 7, 1988), and Aldrich Catalog,[1] p. 1005 (Ans. 8).

Claim 1 is representative and reads as follows:

1. A method for formulating an enzyme comprising:
obtaining a library of glucose oxidase genes;
creating a library of mutated glucose oxidase genes;
introducing each mutated glucose oxidase gene of the library into separate expression vectors;
inserting the expression vectors into non-human host organisms;
growing colonies of the host organisms; and
screening the colonies for predefined, desired properties by determining whether the colonies contain active glucose oxidase and determining whether the colonies have predefined, desired peroxide resistant properties,
wherein determining whether the colonies have predefined, desired peroxide resistant properties comprises:
incubating the colonies in peroxide; and
determining whether the colonies have active glucose oxidase after incubating the colonies in peroxide.

ISSUES ON APPEAL

The issues in this appeal are as follows:

Did the Examiner err in determining that it would have been obvious to persons of ordinary skill in the art to apply Cherry's genetic engineering technique for selecting mutant peroxidase enzymes to glucose oxidase?

Does Valdes "teach away" from using Cherry's genetic engineering technique to solve the glucose oxidase stability problem because Valdes

[1] As noted by Appellants, the Examiner did not include "Aldrich" in the main statement of the rejection, but referred to it when describing the grounds of the rejection (App. Br. 7).

teaches a different direction and "entirely different" approach than utilized by Cherry?

PRINCIPLES OF LAW

"Often, it will be necessary . . . to look to interrelated teachings of multiple [references] . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "[T]his analysis should be made explicit," and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.*

An obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.*

In assessing a claim's obviousness, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416.

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development

> flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

"[A] reference may teach away from a use when that use would render the result inoperable." *In re ICON Health and Fitness Inc.*, 496 F.3d 1374, 1381 (Fed. Cir. 2007).

FINDINGS OF FACT

Valdes

1. Valdes teaches that it has been proposed that glucose oxidase, commonly used in glucose sensors, deactivates over time due to hydrogen peroxide, a byproduct of the enzymatic reaction (Valdes, at 367-68 & 372-73).

2. Valdes teaches that GO deactivation can lead to failure of glucose sensors and describes different approaches to protect the enzyme (*id.* at 367-68).

3. Valdes states that "[b]etter options [to protect GO], however, are to simply prevent the degradation of the enzyme using other chemical agents, or techniques." (*Id.* at 375.)

4. As an example, Valdes describes immobilizing catalase with GO because "catalase is the natural hydrogen peroxide destroying catalyst" (*id.*).

5. Valdes also describes avoiding hydrogen peroxide degradation by using supports which deactivate the peroxide (*id.*).

6. Valdes concludes that "[f]urther research is therefore needed to make GO[ ] less sensitive to H_2O_2 degradation" (*id.*).

Cherry

7. Cherry describes the use of enzymes as catalysts in commercial and industrial applications: "As chemical catalysts are typically used under conditions considerably different, and often harsher, than those found in the environment, this will require enzymes that have been genetically altered to

improve their performance under defined, application-specific conditions." (Cherry, 379, col. 1).

8. Cherry refers to a review which "cites a number of examples of the in vitro evolution of enzymes from relatively ineffective catalysts to commercially viable products by a variety of directed evolution techniques" (*id.* at 379, col. 1; see also *id.* at 383, col. 2).

9. Cherry describes mutagenesis of a peroxidase enzyme to produce mutants with greater temperature stability and resistance to oxidative damage by hydrogen peroxide (*id.* at 382-83; at 383 ("Discussion")).

Hatzinikolaou

10. Hatzinikolaou describes isolation and cloning of a new glucose oxidase from Asperigillus niger (Hatzinikolaou, 371).

ANALYSIS

Claim 1 is drawn to a multi-step genetic engineering method involving mutating a glucose oxidase gene and then screening for mutants with "peroxide resistant properties." The Examiner found that Cherry described a genetic engineering method for producing enzymes resistant to hydrogen peroxide having steps as recited in claim 1, with the difference that Cherry performed the method on a peroxidase enzyme, not glucose oxidase as claimed (Ans. 5-6). However, the Examiner found that Valdes had identified peroxide deactivation as a problem associated with glucose sensor failure (*id.* at 5). The Examiner determined that persons of ordinary skill in the art would have had reason to apply Cherry's technique to Valdes' glucose oxidase enzyme to generate a mutant resistant to hydrogen peroxide, solving the problem articulated in the Valdes publication (*id.* at 6-7).

Appellants contend that the Examiner erred in this determination. They argue that the prior art does not teach or suggest the claimed invention, but rather teaches away from it. They contend that "[n]either Valdes et al., nor any prior art of record that relates to peroxide degredation [sic] of glucose oxidase, describe or suggest the use of a gene mutation method for addressing peroxide degredation [sic] of glucose oxidase." (App. Br. 10).

In making an obviousness determination, the Examiner is not required to identify explicit teachings in the prior art that would have led persons of ordinary skill in the art to the claimed subject matter. *KSR*, 550 U.S. at 418. Rather, as long as the Examiner provides a plausible reason as to why the skilled worker would have been prompted to have made the claimed invention, his burden is met. *KSR*, 550 U.S. at 418.

In this case, although Valdes made no mention of genetic engineering techniques to solve the GO stability problem, the Examiner properly took "account of the inferences and creative steps that a person of ordinary skill in the art would employ," and reasoned that the skilled worker would have found it obvious to apply Cherry's technique for producing peroxidase resistance to the GO enzyme. *Id.* The Examiner's determination is supported by evidence because Cherry explicitly acknowledged the value of its genetic engineering technique to improve enzyme performance in commercial and industrial applications (FF 7-8). Persons of ordinary skill in the art therefore would have reasonably extrapolated Cherry's teaching to solve the glucose oxidase problem posed by Valdes.

Appellants contend that Valdes refers to conventional methods, such as using additives for deactivating hydrogen peroxide or other chemical

methods (App. Br. 16), teaching away from using Cherry's genetic engineering technique. Appellants argue:

> More specifically, Valdes et al. refer to completely different directions taken by those most skilled in the art, whereby the glucose oxidase enzyme is immobilized and attached to a support that deactivates peroxide. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999).

(App. Br. 21).

It is undisputed that Valdes proposes chemical, enzymatic, and support techniques for protecting the GO enzyme. However, Valdes' failure to suggest genetic engineering techniques to solve the GO stability problem is not a "teaching away" from the claimed method because merely proposing an approach to a problem, would not have discouraged the skilled worker from taking other approaches, particularly when such approaches had been suggested by the prior art and shown to be successful in related systems.

Claims 6-8, 10, 11, 16, 17 and 46 are rejected over Valdes, Cherry, and Hatzinikolaou as for claim 1, and further in view of other cited prior art. Appellants challenge the rejections only to the extent that Valdes, Cherry, and Hatzinikolaou do not each or suggested the claimed method. As we have already found these arguments deficient for claim 1, we affirm the additional rejections for the reasons cited by the Examiner.

CONCLUSIONS OF LAW & SUMMARY

The Examiner did not err in determining that it would have been obvious to persons of ordinary skill in the art to apply Cherry's genetic engineering technique to glucose oxidase in order to select for mutants with peroxide resistant properties. Valdes did not "teach away" from using Cherry's genetic engineering technique to solve the glucose oxidase stability problem identified by Valdes. The obviousness rejection of claim 1 is affirmed. Claims 3-5, 12-15, 18-24, 44, and 45 fall with claim 1 because separate reasons for their patentability were not presented. 37 C.F.R. § 41.37(c)(1)(vii).

As Appellants rely on the arguments made with respect to claim 1 as to the remaining rejections, we also affirm the rejection of

claims 16 and 17 under 35 U.S.C. § 103(a) as obvious in view of Valdes, Cherry, Hatzinikolaou, and Misonix; and

claims 6-8, 10, 11, and 46 under 35 U.S.C. § 103(a) as obvious in view of Valdes, Cherry, Hatzinikolaou, Wagner, and Aldrich Catalog.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

alw

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